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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/120,030	07/21/1998	BETH P GOLDSTEIN	7732-022-27	1743

23552 7590 10/30/2006

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ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 10/30/2006

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/120,030
Filing Date: July 21, 1998
Appellant(s): GOLDSTEIN ET AL.

Steven V. Kelber
For Appellant

Supplemental EXAMINER'S ANSWER

This Supplemental Examiner's Answer is prepared to include Dixon et al. reference in the list of Evidence Relied Upon.

This is in response to the appeal brief filed 02/02/2006 appealing from the Office action mailed 09/17/2004.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Zygmunt et al. Progress in Drug Research, 16, 309-333, 1972

Stark et al. N.Engl. J. Med, 291, 239-240, 1974

Goldberg et al. Antimicrob. Ag. Chemother., 45-53, 1967

Oldham et al. J. Dairy Sci., 74, 4175-4182, 1991

Dixon et al. Yale J. Physiology and Medicine, 41, 62-68, 1968

(9) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims.

It was noticed that claims 56,58,59 which require presence of second antibiotic were inadvertently placed together with claims 4,5,32,44-51,58, and 61-66 in the first rejection of record. Rather, these claims should have been placed together with claims 32,46,47,50,51 in the second rejection of record which adds secondary reference to address the use of second antibiotic. The proper grouping of claims is reflected in the rejections below.

A. Claims 4,5,32,44-51,57, and 61-66 are rejected under 35 U.S.C. 103(a) as unpatentable over Zygmunt, and Goldberg and Stark, and further in view of Oldham.

The instant claims are drawn to method of treating staphylococcal infection comprising systemic administration of a recombinantly produced lysostaphin analogue, wherein multiple doses of the lysostaphin analogue are administered, and wherein the amount of the lysostaphin analogue is from 0.5 to 30 mg/kg/day. Base claim 1 is directed to treatment of infection in organs; base claim 2 is directed to treatment of infection associated with catheter or prosthetic device.

Zygmunt

Zygmunt et al is a general reference reviewing properties of lysostaphin, its *in vitro* and *in vivo* applications, and various ways of administration. The reference teaches

that lysostaphin is effective against a wide variety of staphylococcal infection, and is more potent than penicillins. The reference describes treatment of staphylococcal infections in various organs, such as kidney, heart valve (pages 319-325). The ways of administration are both systemic and topical (pages 319-324). The dosages of lysostaphin vary depending on the ways of administration; thus reference cites use of single doses in the range of 0.5 to 50 mg/kg (p. 320, Table 4), or multiple doses in the range of 0.5 to 50 (p.523, bottom addressing study of Goldberg et al; see discussion of Goldberg reference below). Thus, both the dosage and ways of administration are result-effective variables which may be optimized by an artisan in a course of routine optimization. Combined therapy with other antimicrobials, such as methicillin, augments effect of lysostaphin (p. 322). The reference also teaches pharmaceutical compositions comprising lysostaphin.

Goldberg

Goldberg et al teach treatment of staphylococcal infection in dogs with lysostaphin used intravenously at dosages 5-50 mg/kg. The administration was done multiple times, at intervals 1 to 24h. Treatment courses consisted of 1 to 23 injections over periods of 5h to 6.5 days. When recalculated to the amounts in mg/kg/day, i.e., as used in the instant claims, dogs 4, 5, 7, and 10 received 35.4, 31.6, 17.6, and 13 mg/kg/day, respectively [1]. Although lysostaphin administration was followed in relapse in some dogs (dogs 7 and 10), administration of lysostaphin caused from substantial

reduction to complete clearance of infection. See Table 1. Lysostaphin treatment was effective in treatment of infection in lung, liver, spleen, kidney, and aortic and mitral valves. Heart valves were the most easily sterilized tissue. Adverse reactions to lysostaphin were not observed. See abstract and Table 1.

Note, that the amount of lysostaphin which resulted in successful treatment of dogs (no relapse) of dogs 4 and 5 (Table 4), is only marginally different from the claimed amount of up to 30 mg/kg/day of recombinantly produced lysostaphin for treatment of humans as claimed in claims 4,5, or up to 25 mg/kg/day as claimed in claims 45-47. See further discussion in the Response to Arguments below

Zygmunt and Goldberg references do not teach administration of lysostaphin to humans.

Stark (N.Engl. J. Med, 291, 239-240, 1974; see specification, p. 3, lines 21-25).

Stark et al describes systemic administration of lysostaphin to a man suffering from staphylococcal pneumonia resulting from terminal unresponsive leukemia. The reference demonstrates that parenteral systemic administration of lysostaphin reduces bacteremia caused by strain of S. *Aureus* which proved to be resistant to methicillin, vancomycin and cephalothin. Single treatment with lysostaphin resulted in a complete clearance of microorganisms from pustule sites. The treatment also removed staphylococci from blood, lungs, or abscess site.

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1 All amounts hereinafter are recalculated into mg/kg/day as (Mean dose)x(No. doses)/(No days

Therefore, the prior art teaches that lysostaphin is effective both *in vitro*, in animal studies, and in humans. In regard to multiple administration to humans, as Goldberg teaches that lysostaphin is effective in animal studies when taken either in a single dose or repetitively, it would be obvious to select an appropriate regime of administration in humans as well. In regard to the particular dosage ranges, first, Goldberg teaches dosage range that overlaps with the claimed dosage ranges. Second, if there are any differences between dosage ranges as claimed and that of the prior art, the differences would be appear minor in nature; in addition as the dosage is an result-effective variable, as can be clearly seen from, e.g., Goldberg, selection of the dosage, protocol and route of administration will be obvious to one skilled in the art as a result of routine optimization.

The references above do not teach recombinant lysostaphin or use thereof. It is well established in the art that recombinant way of production of proteins is easier and more effective than non-recombinant methods (such as organic synthesis or purification). Oldham reference is used to demonstrate that lysostaphin can be produced recombinantly and that the product produced thereby has high antimicrobial activity similar to that of the natural product.

Oldham

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treated) as suggested by applicant in response filed 10/20/2003

Oldham et al teaches that lysostaphin can be produced recombinantly and demonstrates that recombinant lysostaphin, at low concentration of 5 μg/ml, is effective against *S. Aureus* in mammary tissue. See abstract. Note that administration to mammary tissue reads on the instantly claimed systemic administration, as the latter encompasses direct delivery to organs through injection (see specification, page 6, lines 31-32)

It would have been obvious to one skilled in the art at the time the invention was made to be motivated to use recombinant lysostaphin instead of the natural lysostaphin used in the primary references (e.g., in the systemic treatment described by Stark et al. or Goldberg et al.), because it is easier to produce a recombinant analog of a natural product and because Oldham demonstrated that recombinant lysostaphin has high antimicrobial activity, similar to the natural product. Further, there is no evidence that lysostaphin produced recombinantly (i.e., natural lysostaphin recreated recombinantly) is any different from natural lysostaphin.

Further, in regard to lysostaphin analogs and use thereof, it is well known in the pharmaceutical art to develop and use new, improved analogs of known pharmaceuticals. As mechanism of action of lysostaphin is the lysis of the membrane wall of staphylococci, it would be obvious to develop and use new, more potent analogs of this well known antibiotic. Specification, p. 1, lines 26-34, is cited to exemplify lysostaphin analogs known in the prior art.

In regard to various locations of treatment, as Zygmunt teaches that lysostaphin is effective against more than 300 staphylococcus species and suggests its wide use at various locations, and as Stark suggests use of lysostaphin for treatment of human staphylococcal infections in lung, liver, brain, endocardium, and bone, it would have been obvious to an artisan to apply this versatile antimicrobial at the sites which require antimicrobial treatment with the expectation, in the absence of evidence to the contrary, that such treatment will be successful.

B. Claims 32,46,47,50,51,56,58,59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zygmunt, Goldberg Stark, and Oldham as applied above, and further in view of Dixon.

The instant claims are drawn to combination therapy of lysostaphin and another antimicrobial, in particular rifamycin or a glycopeptide.

The primary references do not teach combined use of lysostaphin and rifamycin or a glycopeptide. However, Zygmunt teaches that lysostaphin is effective against staphylococcal infection only for limited time, and it is preferable to follow lysostaphin with another antibiotic. Dixon et al. teach that it is preferable to use lysostaphin in combination with other antimicrobials because a single dose usage of lysostaphin reduces dangers of hypersensitivity reaction. See p. 63, first paragraph. Because combination therapies for treatment of staphylococcal infection are well-known in the art and because it would have been desirable to use plural therapies in order to maximize the probability that staphylococcal infection is minimized, it would be *prima facie*

obvious to one of ordinary skills in the art at the time the invention was made to be motivated to use the lysostaphin not only as a sole active pharmaceutical agent, but also in combination with other commonly used antimicrobials, such as rifamycin or glycopeptides.

(10) Response to Argument

A. Rejection of claims 4,5,32,44-51,57, and 61-66 under 35 U.S.C. 103(a) as unpatentable over Zygmunt, and Goldberg and Stark, and further in view of Oldham.

In regard to Goldberg reference, appellant argues that the dosage effective in dogs was outside of the dosage range as instantly claimed. In particular, appellant points out that compared to the top limit of 30mg/kg/day in humans, the dosage described by Goldberg for dogs that demonstrated full improvement is "as high as" 31.6 or 35.4 mg/kg/day for dogs 5 and 4, respectively. The dosages of less than 30mg/kg/day were initially effective but then was followed by relapse (e.g., dogs 7, 10).

Examiner disagrees for the following reasons:

(1) There is only a marginal difference between dosages described as effective on dogs in Goldberg and dosage range as instantly claimed. Compare, for example 31.6 or 35.4 mg/kg/day for dogs 5 and 4, respectively, with 30 mg/kg/day as claimed. The dosage is in the same order, and it would be *prima facie* to an artisan that dosage

demonstrated to be effective in dogs should be fine-tuned for use in humans. As the dosage is an result-effective variable as can be clearly seen from Goldberg, selection of the dosage, protocol and route of administration would be obvious to one skilled in the art as a result of routine optimization. Thus, absent some teaching to the contrary (which is not offered by appellant), determination of particular ranges employed is within the skill of the ordinary worker as a part of the process of normal optimization.

(2) Note also, that Goldberg used amounts of lysostaphin which are well inside the claimed range: 17.6, and 13 mg/kg/day for dogs 7 and 10. Although the infection relapsed in these dogs, the instant claims are not excluding relapsing; rather, they are merely directed to "treatment" of the infection. Note that for the dog 10 that received the smallest amount, 10 mg/kg/day, the amount of colonies/ml of blood dropped from 4,520 to just 16 in 2 hours. See Table 1.

(2) It is well known that actual activity of antibiotics is batch-dependent - this is why activity of antibiotics is often expressed in units of activity, rather[2] than in absolute units like mg/kg/day as in the instant claims - and, again, it would be obvious that determination of particular ranges of recombinant lysostaphin for use in humans would be within the skill of the ordinary worker as a part of the process of normal optimization.

(3) As the instant claims are drawn to recombinant lysostaphin, and Oldham demonstrated that recombinant lysostaphin has antimicrobial activity similar to the

[2]See, for example Schuhardt et al. J. Bacteriol., vol. 88, 1964, p. 815, lines 4-8.

natural product, it would be obvious, again, that the dosage of recombinant lysostaphin albeit being in the same range as natural lysostaphin, would have to be fine-tuned.

(4) Finally, instant specification itself supports the obviousness to determine a particular dosage range as it states that "suitable dosages and regiments of lysostaphin may vary with the severity of infection and the sensitivity of the infecting organism" (see p. 10, lines 5-9).

With regard to appellant's argument that Goldberg teaches away from administering amounts of lysostaphin as instantly claimed because the reference allegedly demonstrates that repeated exposure to small amounts of lysostaphin causes development of resistant strains and eventual relapse of the dogs: The instant claims are not directed to individual doses, but rather to overall amount administered per day. From this point of view, there is no clear indication in the reference that the lower the daily amount the more probable is development of resistant strains and eventual relapse of the dogs. Contrary, looking at Table 4, dog 6 receiving much higher amount of lysostaphin (57 mg/kg/day) demonstrates about the same or higher amount of resistant strains in blood and tissue than dogs 7 and 10 that received much lower, 17mg/kg/day and 13 mg/kg/day, amounts respectively. Further, as addressed above, the instant claims are not excluding relapsing; rather, they are merely directed to "treatment" of the infection.

With regard to Stark reference, appellant argues that the study was done on a single human, and the patient eventually died. First, the cause of death of the patient

can be unrelated to the antimicrobial treatment (the patient suffered from unresponsive leukemia). Second, the reason the reference was used was to demonstrate that systemic administration of lysostaphin to a human is known in the art. Further, note that the reference demonstrates that just a single treatment with lysostaphin resulted in a complete clearance of microorganisms from pustule sites.

With regard to the use of Oldham reference the sole purpose of citing the reference was to demonstrate that this antibiotic can be produced recombinantly and that it does indeed demonstrate antimicrobial activity.

With regard to claims 44-51 (section 2, page 9 of the Brief), appellant argues that the claims are separately patentable because the amount of *up to 25 mg/kg/day* is "substantially lower" than the dosages administered in Goldberg. Examiner disagrees. First, Examiner does not view 25 mg/kg/day as being "substantially lower" from, e.g., 31.6 mg/kg/day for dog 5 in the reference. Neither the instant specification draws such distinction; contrary, the range described in the specification (and as previously claimed) is 0.5-50 mg/kg/day. Second, as discussed above dogs 7 and 10 received 17.6 and 13 mg/kg/day, respectively, i.e., well within the range instantly claimed. and, although lysostaphin administration was followed by a relapse, administration of lysostaphin caused from a substantial reduction to complete clearance of infection.

With regard to claims 61-64, appellant argues that the claims are separately patentable because they claim either that the infection is cleared or that treatment

results in complete sterilization of the infection. First, claims 61,63 do not claim "complete sterilization"; as to being "cleared", this relative term does not mean complete removal and all the cited prior art teaches removal of, and thus clearance from, the infection. As for claims 62, 64, both Goldberg, on dogs, and Stark, on human, demonstrate a "complete sterilization" achieved at least for some time and at least in one site. Thus, Goldberg teaches complete removal of colonies from aortic and mitral valves (see results for dogs 4 and 5 in Table 1), and Stark demonstrates complete clearance of microorganisms from pustule sites.

B. Rejection of claims 32,46,47,50,51,56,58,59 under 35 U.S.C. 103(a) as being unpatentable over Zygmunt, Goldberg Stark, and Oldham, and further in view of Dixon.

Appellant argues that Dixon reference does not remedy deficiencies of other reference. Examiner maintains that combination of references of Zygmunt, Goldberg Stark, and Oldham is applicable for the reasons discussed above. As for the combination of lysostaphin with other antimicrobials, Examiner maintains that it would be obvious to use the lysostaphin not only as a sole active pharmaceutical agent, but also in combination with other commonly used antimicrobials because combination therapies for treatment of staphylococcal infection are well-known in the art and because it would have been desirable to use plural therapies in order to maximize the probability of eradicating staphylococcal infection.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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